PANDAS and PANS: Clinical, Neuropsychological, and Biological Characterization of a Monocentric Series of Patients and Proposal for a Diagnostic Protocol

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Abstract

Objectives: Whether PANS (pediatric acute-onset neuropsychiatric syndrome) and PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) represent true clinical entities is debated and data for a characteristic phenotype are still controversial. In this study, we aim to characterize clinical, neuropsychological, and biochemical aspects in a sample of PANS and PANDAS patients.

Methods: Patients fulfilling a clinical diagnosis of PANS or PANDAS from 2014 to 2017 were enrolled. Neurological and psychiatric examination and biochemical and instrumental assessment results were collected. A neuropsychological battery was administered. For comparison purposes, a control group of patients with Sydenham's chorea (SC) was evaluated. Descriptive and comparative statistical analyses were performed.

Results: Seven subjects received a diagnosis of PANS, 12 of PANDAS, and 11 of SC. Clinical presentation of PANS children showed statistically significant differences compared with both PANDAS and SC, in particular, with the presence of obsessive symptoms, behavioral regression, and somatic symptoms in the first group. Moreover, all PANS patients showed some neuropsychological deficits in visual-motor abilities, short- and long-term memory, and processing speed.

Conclusions: Our experience confirms that patients with PANS had a complex clinical presentation and a compromised neuropsychological profile with respect to patients with PANDAS or SC. However, the absence of biological markers or instrumental alterations made the diagnosis of the two entities, PANS and PANDAS, a matter of exclusion. For these reasons, we propose a pilot diagnostic protocol that (when applied in a prospective manner) will allow comparison with similar childhood-onset neuropsychiatric disorders, such as obsessive-compulsive or tic disorders, and efficacy evaluation of different therapeutic approaches.

Keywords: PANS (Pediatric Acute-onset Neuropsychiatric Syndrome), PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection), Group A Streptococcus, Sydenham's chorea

Introduction

THE TERM PEDIATRIC AUTOIMMUNE neuropsychiatric disorders associated with streptococcal infection (PANDAS) was defined by Swedo et al. in 1998 to describe a group of 50 children with a sudden onset of obsessive-compulsive disorder (OCD) and tic disorders triggered by group A beta-hemolytic streptococcal (GABHS) infection. Since the first description, Swedo et al. (1998) highlight that these children manifested also emotional lability,

separation anxiety, deterioration in handwriting, and personality change.

The natural history of the disease was similar to that of Sydenham's chorea (SC), but without any systemic involvement. The exact pathophysiology is not fully understood: a major hypothesis is molecular mimicry where antibodies produced against streptococcal proteins also find a target in brain proteins, particularly in the basal ganglia, similar to SC (Cunningham 2016). Interestingly, SC patients often exhibit OCD, emotional lability, and anxiety

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symptoms at the same time or before the onset of movement disorder (Punukollu et al. 2016).

Since its first description, PANDAS has been considered a controversial diagnosis, both on clinical and autoimmune bases (Dale et al. 2006; Leckman et al. 2011).

Its existence as a distinctive entity, given the difficulty in establishing a tight link between the streptococcal infection and the onset or recrudescence of neuropsychiatric symptoms and the lack of biological markers, is still debated (Orefici et al. 2016).

These difficulties led to a revision of clinical features and diagnostic criteria, and the authors proposed a new clinical entity called PANS, pediatric acute-onset neuropsychiatric syndrome, characterized by abrupt-onset OCD and/or restricted food intake with concurrent presence of neuropsychiatric symptoms after an infectious or environmental trigger (Swedo et al. 2012). PANDAS would be considered a subset of PANS.

Clinical and pathophysiological definitions of PANDAS and PANS are crucial and affect treatment aspects since these patients may benefit from antibiotic and immunomodulatory treatments along with symptomatic treatment (Snider et al. 2005; Williams et al. 2016).

The objective of the present research was to describe clinical, biological, and psychological features of a group of patients fulfilling the clinical criteria of PANDAS and PANS referred to our hospital. In particular, we search for a characteristic neurocognitive endophenotype that could be of help in identifying disorders and has not yet been clearly defined. As patients with SC demonstrate overlapping psychiatric symptomatology and similar pathophysiology, we compare the results with those of a group of SC patients.

Afterward, we propose a diagnostic protocol that may help in differential diagnosis and in identifying efficacy of different treatment pathways.

Methods

Participants

Participants were recruited at the Neuropsychiatric Unit of Giannina Gaslini Institute in Genoa.

Three groups of subjects were included in the present study:

1. The first group consisted of seven children (mean age 7.7 years $\pm$ 2.43) with clinical diagnosis of PANS (PANS group), using clinical criteria described by Swedo et al. (2012). All children in this group had acute onset of OCD.
2. The second group consisted of 12 children (mean age 6.3 years $\pm$ 1.54) with clinical diagnosis of PANDAS (PANDAS group), using Swedo's diagnostic criteria (Swedo et al. 1998). All patients (12/12) had vocal or motor tics and 2/12 children also had OCD.
3. The third group consisted of 11 children (mean age 9.9 years $\pm$ 1.73) with clinical diagnosis of SC. SC was diagnosed according to the modified Jones criteria for rheumatic fever (Guidelines for the diagnosis of Rheumatic Fever, Jones Criteria, 1992). All children underwent a cardiac evaluation, which showed suggestive cardiological anomalies, and a rheumatological evaluation; 7/11 patients exhibited a monophasic type and 4/11 patients had recurrence of neurological symptoms.

Due to the noninterventive study design, no informed consent form was requested.

Clinical history and tests

Neurological examination, laboratory tests, brain magnetic resonance imaging (MRI), and electroencephalography (EEG) were performed during a flare-up for children with PANS or PANDAS or at disease onset for patients with SC.

A full medical history, including symptoms at disease onset, exposure to infections, episodes of fever, the presence of psychiatric disorders, autoimmune and movement disorders, and family history, was collected with caregivers at first evaluation.

Physical and neurological examinations were carried out by a child neuropsychiatrist with expertise in movement and psychiatric disorders (Dr. Elisa De Grandis).

Laboratory tests for infection included C-reactive protein (CRP), anti-streptolysin O (ASO), anti-deoxyribonuclease B (anti-DNAse B), and nasal and throat swabs. Laboratory thresholds used to suggest a previous streptococcal infection were 200 international units (IU)/mL for ASO and 150 IU/mL for anti-DNAse B.

Psychological evaluation was performed by an expert psychologist by means of age-standardized tests (Table 1) (Leckman et al. 1989; Wechsler 1991, 2005; Scahill et al. 1997; March 2012).

Brain MRI was performed using a 1.5-Tesla magnetic resonance scanner, consisting of 3-mm-thick T1- and T2-weighted imaging, fluid-attenuated inversion recovery, and diffusion-weighted images on three planes. Imaging studies were evaluated by an expert pediatric neuroradiologist.

Electroencephalography was performed at first evaluation using a computerized electroencephalographic system (Galileo System, 98 EBNeuro, Florence, Italy). Scalp electrodes were positioned according to the international 10–20 system. Mean duration was 40 ± 10 minutes for the EEG recording.

Statistical analysis

Data are described as mean and standard deviation or median and range for continuous variables and as absolute and relative frequencies for categorical variables.

A nonparametric analysis (Mann–Whitney *U*-test, Kruskal–Wallis test) for continuous variables and the chi-square or Fisher's exact test for categorical variables were used to measure differences between groups.

p Values ≤ 0.05 were considered statistically significant, and all *p* values were based on two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS, Inc., Chicago, IL).

Results

Demographics and clinical features

Thirty children (12 males and 18 females) were included overall in our study, according to clinical diagnosis. Seven children (2 males and 5 females) received a diagnosis of PANS and 12 children (7 males and 5 females) received a diagnosis of PANDAS. The SC group consisted of 11 patients (3 males and 8 females). Clinical and epidemiological data are summarized in Table 2.

Three of 7 (42.9%) subjects in the PANS group showed previous neuropsychiatric problems (autism spectrum disorder in 2 patients and sleep disorder in 1) compared with 5/12 (41.7%) cases in the PANDAS group (slight psychomotor delay in 2 children, epilepsy in 1, learning disorder in 1, and autism spectrum disorder in 1) and 3/11 (27.3%) children with SC (learning disorder in 2 patients and psychomotor delay in 1). Parents reported the presence of an infectious trigger, followed by the onset of neuropsychiatric symptoms, in

TABLE 1. NEUROPSYCHOLOGICAL TESTS USED IN EVALUATION OF SUBJECTS

Function	Test	Age range and test description
Motor and vocal tics	YGTSS	6 to 17 years—Presence and severity of motor and vocal tics
Obsession and compulsion	CYBOCS	6 to 17 years—Presence and severity of child's obsession and compulsion
Anxiety	MASC	8 to 19 years—Presence and kinds of child's anxiety symptoms
Short-term memory	Digit Span subtest (WISC III-IV)	6 to 16 years—Verbal short-term memory
	Coding subtest (WISC III-IV)	6 to 16 years—Visual-motor dexterity, nonverbal short-term memory
Attention	Symbol Search subtest (WISC III-IV)	6 to 16 years—Accuracy, attention, and concentration
Processing speed	Processing Speed Index (WISC III-IV)	6 to 16 years—Speed of cognitive processes and response output on visual-motor tasks

CYBOCS, Children's Yale-Brown Obsessive Compulsive Scale; MASC, Multidimensional Anxiety Scale for Children; WISC, Wechsler Intelligence Scale for Children; YGTSS, Yale Global Tic Severity Scale.

6/7 (85.7%) children with PANS diagnosis, in 9/12 (75%) patients with PANDAS diagnosis, and in 6/11 (54.5%) SC patients.

No statistical differences in gender, presence of previous neuropsychiatric problems, and psychiatric or autoimmune family history were detected between PANS and PANDAS groups. Autoimmune diseases were most common in first-degree relatives of children with PANDAS and PANS compared with the SC group (both $p=0.04$).

Age at onset of PANS, PANDAS, and SC symptoms (median, range, mean, and standard deviation) is reported in Table 3. No significant difference was detected between PANS and PANDAS groups or PANS and SC groups. Age at onset of PANDAS symptoms was significantly lower compared with movement disorder onset in SC patients ($p=0.0001$).

All patients with PANS (7/7–100%) presented obsessive-compulsive symptoms. None of our patients presented at the onset extreme food restriction.

Neuropsychiatric symptoms at onset in PANS, PANDAS, and SC groups are reported in Table 2. In PANS patients, obsessive-compulsive symptoms ($p=0.01$), behavioral regression ($p=0.04$), and somatic symptoms ($p=0.02$) were significantly more common

than in children with clinical diagnosis of PANDAS. When comparing PANS clinical presentation with SC clinical features, obsessive-compulsive symptoms ($p=0.004$), irritability ($p=0.01$), behavioral regression ($p=0.01$), sensory and motor abnormalities ($p=0.01$), and especially somatic symptoms ($p=0.0001$) were significantly more common in PANS patients (Table 2).

Laboratory tests

Pharyngeal and/or nasal swabs were positive for group A beta-hemolytic *Streptococcus* in 2/7 (28.6%) patients with PANS and in 5/12 (41.7%) patients with PANDAS.

ASO mean values in the three patients' groups are reported in Table 3.

No significant difference was found between ASO values in PANS and PANDAS children. In the SC group, the mean value of ASO was significantly higher than in PANS ($p=0.003$) and PANDAS groups ($p=0.002$).

The ASO value resulted higher than the reference value of our laboratory (i.e., >200 IU/mL) in 6/7 (85.7%) PANS children, in 11/12 (91.6%) PANDAS children, and in 11/11 (100%) SC patients.

TABLE 2. CLINICAL AND EPIDEMIOLOGICAL FEATURES

	PANS, N = 7, (%)	PANDAS, N = 12, (%)	Sydenham's chorea, N = 11, (%)	p		
				PANS vs. PANDAS	PANS vs. Chorea	PANDAS vs. Chorea
Gender (male)	2 (28.6)	7 (58.3)	3 (27.3)	0.35	1	0.2
Family history of psychiatric disorders	3 (42.9)	7 (58.3)	2 (18.2)	0.65	0.33	0.09
Family history of autoimmune disorders	3 (42.9)	5 (41.7)	0 (0)	1	0.04	0.04
Perinatal problems	2 (28.6)	2 (16.7)	0 (0)	0.6	0.14	0.48
Previous neuropsychiatric problems	3 (42.9)	5 (41.7)	3 (27.3)	1	0.63	0.67
Obsessive-compulsive symptoms	7 (100)	2 (16.7)	3 (27.3)	0.0007	0.004	0.64
Tics	3 (42.9)	12 (100)	1 (9.1)	0.009	0.24	<0.0001
Anxiety	3 (42.9)	6 (50)	2 (18.2)	1	0.33	0.19
Emotional lability	5 (71.4)	4 (33.3)	5 (45.5)	0.17	0.37	0.68
Irritability	6 (85.7)	7 (58.4)	2 (18.2)	0.33	0.01	0.09
Behavioral regression	4 (57.1)	1 (8.3)	0 (0)	0.04	0.01	1
Worsening of school performance and handwriting	4 (57.1)	4 (33.3)	4 (36.4)	0.38	0.63	1
Sensory and motor abnormalities	4 (57.1)	6 (50)	0 (0)	1	0.01	0.01
Somatic symptoms	6 (85.7)	3 (25)	0 (0)	0.02	0.0004	0.22

Bold values are statistically significant.

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; PANS, pediatric acute-onset neuropsychiatric syndrome.

TABLE 3. LABORATORY TESTS

PANS, N = 7		PANDAS, N = 12		Sydenham's chorea, N = 11		p		
Average $\pm$ SD	Median (rank)	Average $\pm$ SD	Median (rank)	Average $\pm$ SD	Median (rank)	PANS vs. PANDAS	PANS vs. Chorea	PANDAS vs. Chorea
Age at onset (years) 7.7 $\pm$ 2.6	7 (4–12)	6.33 $\pm$ 1.6	6.5 (4–10)	9.9 $\pm$ 1.8	10 (7–13)	0.23	0.08	0.0001
ASO (IU/mL) 313.4 $\pm$ 231.6	257 (94–799)	500.3 $\pm$ 347.2	377 (120–1250)	935.1 $\pm$ 466.7	1125 (298–1600)	0.23	0.003	0.02
Anti-DNAse B (U/mL) 761.6 $\pm$ 536.5	560 (268–1770)	1115.2 $\pm$ 562.4	1220 (201–1970)	1092.9 $\pm$ 934.6	964 (162–3287)	0.25	0.48	0.65

Bold values are statistically significant.

ASO, anti-streptolysin O; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; PANS, pediatric acute-onset neuropsychiatric syndrome; SD, standard deviation.

Anti-DNAse B mean values are reported in Table 3.

The mean value of CRP was <0.46 mg/dL (laboratory reference value) in all the considered groups.

Anti-DNAse B and CRP do not show any statistical differences among the three groups.

Psychological assessment

Psychometric assessment was administered to 24 children overall and in particular to 5 of 7 patients in the PANS group, 9 of 12 patients in the PANDAS group, and 10 of 11 patients in the SC group (Table 4).

Psychological testing was accomplished in SC patients within 1 month of disease onset. All PANS and PANDAS patients were studied during a flare-up. PANS subjects were studied after a median interval of 2 years (range 1–2 years) from disease onset. Three of five patients were receiving intramuscular penicillin, two corticosteroid and intravenous immunoglobulins (IVIGs), and one immunoglobulin.

Two PANS subjects were also receiving symptomatic treatment with neuroleptics. PANDAS patients were evaluated after a median interval of 1.5 years (range 1 month–4 years) while receiving intramuscular penicillin (5/9), amoxicillin (4/9) azithromycin (2/9), and azithromycin and fluoxetine (1/9). See above for further pharmacological details.

The mean value on the *Children's Yale-Brown Obsessive Compulsive Scale* (CYBOCS) in the PANS group was significantly higher than the one obtained in both the SC group (5.9 ± 10 ; $p = 0.02$) and the PANDAS group ($p = 0.02$).

The mean value on the *Yale Global Tic Severity Scale* (YGTSS) in the SC group ($p = 0.02$) was significantly lower compared with PANS ($p = 0.04$) and PANDAS ($p = 0.001$) groups (Table 4).

The presence of anxiety symptoms was assessed by the self-assessment *Multidimensional Anxiety Scale for Children* (MASC). The mean value obtained in the PANS group was 40.5 ± 9.2 , but in this group, only 2/5 subjects were able to complete and tolerate administration of the scale because of their clinical features. The

TABLE 4. PSYCHOLOGICAL ASSESSMENT

PANS, N = 5		PANDAS, N = 9		Sydenham's chorea, N = 10		p		
Average $\pm$ SD	Median (rank)	Average $\pm$ SD	Median (rank)	Average $\pm$ SD	Median (rank)	PANS vs. PANDAS	PANS vs. Chorea	PANDAS vs. Chorea
CYBOCS 23.3 $\pm$ 8.6	26 (8–29)	5.4 $\pm$ 11.4	0 (0–28)	5.89 $\pm$ 10	0 (0–28)	0.02	0.02	0.72
YGTSS 22.4 $\pm$ 15.1	21 (0–40)	23 $\pm$ 9.6	20 (15–45)	3.3 $\pm$ 10	0 (0–30)	0.86	0.04	0.001
WISC IV—Digit Span 5.4 $\pm$ 3.2	5 (1–9)	10.7 $\pm$ 1.8	11 (7–13)	9.7 $\pm$ 2.5	9 (6–13)	0.004	0.03	0.44
WISC IV—Coding 5 $\pm$ 2.2	6 (1–8)	9.8 $\pm$ 2.9	9 (6–16)	9.11 $\pm$ 3	9 (4–14)	0.005	0.03	0.78
WISC IV—Symbol Search 5 $\pm$ 3.7	7 (1–9)	10 $\pm$ 2.7	10.5 (6–14)	9.44 $\pm$ 2.8	10 (65–121)	0.03	0.03	0.66
WISC IV—Processing Speed Index 70.4 $\pm$ 19.3	79 (47–91)	99.9 $\pm$ 13.4	101.5 (79–123)	95.78 $\pm$ 16.3	97	0.008	0.02	0.55

Bold values are statistically significant.

CYBOCS, Children's Yale-Brown Obsessive Compulsive Scale; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; PANS, pediatric acute-onset neuropsychiatric syndrome; WISC, Wechsler Intelligence Scale for Children; YGTSS, Yale Global Tic Severity Scale.

mean values in PANDAS and SC groups were, respectively, 55 ± 23.4 and 57.5 ± 12.8 . Separation and social anxiety (60%) were more common both in PANDAS and in SC children.

With regard to the Wechsler scale, PANS patients scored significantly lower than PANDAS and SC patients in all evaluated subtests (Table 4).

Based on the performance in Digit Span, Coding, and Symbol Search subtests, we evaluated the Elaboration Speed Index for each patient. Patients with PANS exhibited a statistically slower cognition speed than PANDAS children ($p=0.008$) and SC children ($p=0.02$).

No significant differences were detected between PANDAS and SC patients in all evaluated subtests of the Wechsler scale.

Pharmacological treatment in PANS and PANDAS groups

In the PANS group, 4/7 (57.1%) patients received immunomodulatory treatment with IVIGs, 2 g/kg for 3–5 days. A short course of corticosteroid therapy, before immunoglobulin therapy, with dexamethasone pulses [20 mg/(m²·day) for 3 days] was given to two of seven patients (28.6%). Three of 7 (42.8%) patients repeated infusion with IVIGs monthly for 6 months and 1/7 (14.3%) received a single cycle. Because of persisting PANS symptoms, one of seven children started immunosuppression with mycophenolate mofetil. Regarding the antibiotic treatment, 4/7 (57.1%) patients received intramuscular penicillin every 21 days and 5/7 (71.4%) children received cycles of oral antibiotic therapy (all patients with amoxicillin). A symptomatic therapy was given to two of seven (28.6%) children (risperidone or aripiprazole).

In the PANDAS group, no one has received IVIG therapy. Two of 12 (16.7%) patients received corticosteroid treatment in both cases with prednisone. Seven of 12 (58.3%) patients received therapy with intramuscular penicillin every 21 days and 8/12 (66.7%) children received cycles of oral antibiotic therapy, especially 3/12 (25%) with azithromycin and 5/12 (41.7%) with amoxicillin. A symptomatic therapy was given to 2/12 (16.7%) patients (fluoxetine or pimozide).

EEG, cerebral MRI, and cerebrospinal fluid in PANS and PANDAS groups

In the PANS group, video-electroencephalogram (vEEG, 19 electrodes, 10–20 system) monitoring was performed in 6 of 7 patients and it resulted negative in 3/6 (50%) subjects. In three of six subjects (50%), the vEEG showed focal epileptiform abnormalities: in parietal and occipital lobes in one case and in centro-temporal areas in two patients.

In the PANDAS group, vEEG monitoring was performed in 4/12 patients. In 2/4 (50%) subjects, the vEEG was normal. In 1 patient (25%), the vEEG showed focal occipital epileptiform abnormalities, and in the other one (25%), we found focal epileptiform activity in right fronto-temporal areas activated during sleep with an idiopathic focal epilepsy of infancy pattern.

Brain MRI was performed in 6/7 patients in the PANS group: in all subjects (6/6; 100%), MRI was normal. In the PANDAS group, 5/12 patients underwent cerebral MRI, and in this group also, all MRIs (5/5; 100%) were normal.

Cerebrospinal fluid analysis was performed only in two patients with PANS. In both cases, cytochemical and microbiological analyses were normal. A battery of autoantibodies was performed in both cases (antibodies anti-N-methyl-D-aspartate receptor—anti-NMDAR IgG; anti-leucine-rich glioma-inactivated

protein 1—anti-LGI1 IgG; anti-contactin-associated protein 2—CASPR2 IgG; anti-gamma amino-butyric acid B receptor—GABA-B1/2-R IgG; anti-amino-hydroxymethyl isoxazolepropionic acid (AMPA) receptor—anti-GluR1 IgG; anti-AMPA receptor 2—GluR2 IgG; and antivoltage-gated potassium channel complex (anti-VGKC-complex IgG)) without positive results. Anti-central nervous system antibodies (anti-Hu, anti-Yo, anti-Ri, anti-GAD, anti-Cv2, and anti-Ma) were also performed, and in one patient, we detected a weak presence of anti-GAD in the cerebrospinal fluid, but negative in serum.

Discussion

The purpose of our study was to characterize clinical, biological, and psychological features of a cohort of PANS and PANDAS patients.

The relationship between streptococcal infections and neuropsychiatric disorders is a complex question not yet solved.

The diagnosis of PANDAS and PANS is still based exclusively on clinical criteria as an exclusionary diagnosis with respect to other neurological and psychiatric disorders. This important concept was also pointed out during the first PANS Consensus Conference convened in 2013 (Chang et al. 2015).

Most studies tried to differentiate these syndromes from primitive psychiatric disorders such as OCD and tic disorder (Kilbertus et al. 2014; Jaspers-Fayer et al. 2017); however, the absence of biological markers and difficult to characterize unique clinical aspects made diagnoses doubtful and controversial.

Our study confirms uncertain and undefined aspects of PANDAS, with results that are difficult to explain.

We found a significant difference between the age of onset of PANDAS clinical symptoms and SC symptoms. Our results agree with the data available to date concerning the onset of symptoms described by Singer and Loisele (2003) for subjects with PANDAS and by Cardoso et al. (1997) about SC: mean age of 6.33 years $\pm$ 1.6 for the first group and 9.9 years $\pm$ 1.8 for the last. This finding may suggest that these two diseases are different entities and that PANDAS does not represent just a mild type of SC. We may also suppose that developmental factors and age-related vulnerability windows can be decisive to pathogenicity or clinical expression given by the same causal agent. According to some hypotheses, we think that streptococcal infection would represent an environmental trigger decisive to the expression of tic disorders, which are multifactorial conditions with a strong genetic basis (Martino et al. 2011).

With regard to the biological aspect, our findings do not show a significant difference for ASO, anti-DNAse B, and CRP between PANDAS and PANS groups, supporting some studies (Leckman et al. 2011) that have shown little significance of these markers in identifying subjects with PANDAS. Of note, however, the mean value of ASO in the SC group was significantly higher, which confirms a streptococcal etiology even if ASO elevation is not a main criterion for diagnosis of rheumatic fever (Dajani et al. 1993).

Few studies have investigated neuropsychological functions in children with PANDAS and PANS for any endocognitive phenotype related to cortico-subcortical network dysfunction caused by the autoimmune pathway. Consistent with findings evaluating PANDAS patients, we detected deficits in visual-motor skills and visuospatial integration in our sample (Murphy et al. 2015; Hirschtritt et al. 2009; Lewin et al. 2011).

However, evaluation of attention and memory in visuoperception tasks and elaboration speed in the PANDAS group is not significantly

different compared with the SC group. Psycho-diagnostic evaluation fails to distinguish between these two diseases.

With regard to PANS, our experience confirms a complex clinical presentation. A wide range of other previously reported symptoms (Murphy et al. 2015) were also found in our sample.

In PANS patients, irritability, behavioral regression, handwriting deterioration, and somatic symptoms (sleep and urinary disorders) show a clear association with main symptoms (OCD and food restriction) and seem to be characteristic of the PANS entity. These symptoms are infrequent not only in patients with PANDAS or SC but also in subjects who present with classic OCD (Murphy et al. 2015). Moreover, psychological evaluation of children with clinical diagnosis of PANS showed significant difficulties in visual-motor skills, short memory tasks, attention, and elaboration speed.

To our knowledge, the neuropsychological profile of PANS subjects was partially analyzed only by Murphy et al. (2015): patient with PANS presented deficit in visuospatial and recalling information on a visuospatial constructional ability test (Rey–Osterrieth Complex Figure test). Neuropsychological results in our PANS sample may be due to a higher functional impairment in these kinds of patients compared with the other groups. However, such psychological data support differentiation of the clinical entity, PANS, compared with other disorders.

In this study, extensive neurological investigation, including MRI, EEG, and lumbar puncture, and infectious and rheumatologic analyses have been carried out, especially in PANS patients who had severe–moderate impairment, but no specific alterations were found.

TABLE 5. EVALUATION TO BE PERFORMED IN ALL PATIENTS WITH SUSPECTED PANS OR PANDAS AT THE MOMENT OF DIAGNOSIS AND REPEATED AFTER 6 AND 12 MONTHS

Medical history
Family history of psychiatric diseases, movement disorders, and autoimmune diseases
Infectious disease evaluation
Assessment of symptoms
Physical examination
Neurological and psychiatric examinations with regard to PANS/PANDAS psychiatric and somatic symptoms and signs
Psychological assessment
YGTSS to assess motor/vocal tics
CYBOCS to assess obsessions and compulsions
MASC for anxiety symptoms
Child Behavior Checklist for behavioral problems
Wechsler Intelligence Scale for children to determine elaboration speed and working memory
Bender Gestalt Motor Visual Test for visuomotor skills
Tower of London for executive functions
Laboratory tests
Complete blood cell count
C-reactive protein
Throat culture
ASO and anti-DNAse B
Immunoglobulin profiles (IgM, IgG subclasses, and IgA)
Urinalysis
Electroencephalogram

ASO, anti-streptolysin O; CYBOCS, Children's Yale–Brown Obsessive Compulsive Scale; MASC, Multidimensional Anxiety Scale for Children; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; PANS, pediatric acute-onset neuropsychiatric syndrome; YGTSS, Yale Global Tic Severity Scale.

To date, the biggest limitation of the diagnosis of these pathologies is the absence of specific biological markers. Nevertheless, we cannot exclude the hypothesis that our PANS patients suffer from autoimmune encephalitis/encephalopathy, in which instrumental examinations and autoantibody patterns did not help in identifying the underlying pathological mechanism. Indeed, it is well known that the clinical and instrumental diagnosis of these disorders could be challenging, leading clinicians to perform a diagnosis of solely probable autoimmune encephalitis (Hermetter et al. 2018).

Given these diagnostic difficulties and based on our experience and literature review (Chang et al. 2015; Orefici et al. 2016; Hermetter et al. 2018), we propose a clinical, instrumental, and psychological operational diagnostic protocol (Tables 5 and 6). With respect to the previously published PANS diagnostic guidelines by Chang et al. (2015), our protocol does not completely fulfill the task of excluding other diagnoses (i.e., complete rheumatologic workup is not included). Our protocol mainly concentrates on diagnosed PANDAS/PANS patients and their neuropsychological phenotype.

TABLE 6. EVALUATION TO BE CONSIDERED WHEN THE PATIENT HAS SEVERE FUNCTIONAL IMPAIRMENT AND WITH RESPECT TO OTHER CLINICAL SYMPTOMS

Brain magnetic resonance imaging
Lumbar puncture
Cerebrospinal fluid parameters (compared with serum levels):
Glucose
Total proteins
Total IgG
Albumin
Cell count
Link index
Oligoclonal bands
Infectious disease evaluation of serum and cerebrospinal fluid
Markers of:
Epstein–Barr Virus
Cytomegalovirus
Human Herpes Virus 6 and Human Herpes Virus 1–2
Adenovirus
<i>Mycoplasma pneumoniae</i>
<i>Borrelia burgdorferi</i>
Varicella-Zoster Virus
Enterovirus
Neuronal antibody testing in serum and cerebrospinal fluid
Anti-N-methyl-D-aspartate receptor antibodies—anti-NMDAR IgG
Anti-leucine-rich glioma-inactivated protein 1—anti-LGI1 IgG
Anti-contactin-associated protein 2—CASPR2 IgG
Anti-gamma amino-butyric acid B receptor—GABA-B1/2-R IgG
Anti-amino-hydroxymethyl isoxazolepropionic acid (AMPA) receptor—anti-GluR1 IgG
Anti-amino-hydroxymethyl isoxazolepropionic acid (AMPA) receptor 2—GluR2 IgG
Anti-voltage-gated potassium channel complex—anti-VGKC-complex IgG
Anti-basal ganglia antibodies—ABGA
Anti-Hu
Anti-Yo
Anti-Ri
Anti-Tr
Anti-GAD
Anti-Cv2
Anti-Ma
Anti-thyroglobulin and anti-thyroperoxidase

For its operational purpose, it has been designed to be administered in a prospective manner to help the clinician in confirming the diagnosis over time and identifying different groups of patients responding to different treatment strategies (psychotropic vs. immunomodulatory), a crucial item in PANS/PANDAS subjects' management.

Limitations and future perspectives

There are several limitations that are worthy of note. It is represented by a small sample size, which may result in an inconsistent and sometimes incomplete representation of these clinical entities.

About psychological assessment, an additional limit is the lack of premorbid data before the disease onset and pharmacological therapy. We are not able to exclude that some deficits in neuropsychological functions may represent an intrinsic vulnerability of the patient or can be influenced by an environmental factor. Moreover, the retrospective nature of parent report of initial symptom onset needs to be considered.

Further prospective studies are needed to elucidate whether or not PANS and PANDAS are true clinical entities and present a characteristic clinical, biological, and neuropsychological phenotype.

Conclusions

Despite these limitations, this study presents clinical, biological, and psychological features of a group of patients fulfilling the PANS and PANDAS criteria and discusses these results in comparison with patients with SC, a well-established clinical condition. Moreover, it adds notable findings to the existing little literature on neuropsychological functioning in youth diagnosed with these disorders, in particular PANS and PANDAS.

Based on these data, we propose a diagnostic protocol to help clinicians in identifying patients and controlling and adapting the correct treatment (Tables 5 and 6). The pilot diagnostic protocol, applied in a prospective manner, will allow comparison with similar childhood-onset neuropsychiatric disorders, such as obsessive-compulsive or tic disorders, and efficacy evaluation of different therapeutic approaches.

Clinical Significance

We describe clinical, biological, and psychological features of a group of patients fulfilling the clinical criteria of PANDAS and PANS referred to our hospital, adding notable findings to existing literature on neuropsychological functioning in youth diagnosed with these disorders. The absence of biological markers or instrumental alterations made the diagnosis of PANS and PANDAS a matter of exclusion, so we propose a pilot protocol to compare their symptoms with similar childhood-onset neuropsychiatric disorders and to evaluate different therapeutic approaches over time.

Disclosures

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